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Vincristine Treatment Triggering the Expression of Asymptomatic Charcot-Marie-Tooth Disease

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A 16-year-old male suffering from Ewing's sarcoma of the pelvis was treated with vincristine as part of his chemotherapeutic protocol. The boy was never known to suffer from any neurological problems. His father had a mild limp, attributed to prolonged "taxi driving," that was never investigated medically. The first course of treatment, which included 2 mg of vincristine, resulted in clinical improvement. However, at the same time the patient developed severe weakness of both upper and lower limbs, areflexia, and gradually a pes cavus deformity. Nerve conduction studies were suggestive of severe peripheral sensorimotor neuropathy, axonal and demyelinative. A definite diagnosis of Charcot-Marie-Tooth was confirmed by molecular analysis showing the typical duplication of 1.5 megabases at chromosome 17 p11.2. This unique manifestation of vincristine neurotoxicity is reported and discussed.

Key words: vincristine, Charcot-Marie-Tooth, PMP-22, PO

INTRODUCTION

Vincristine, a Vinca alkaloid, acts as a mitotic inhibitor [1], comprises a wide spectrum of clinical activity, and is currently administered in the treatment of ALL, Hodgkin's and non-Hodgkin's lymphomas, rhabdomyosarcoma, and other soft tissue sarcomas, osteosarcoma, Ewing's sarcoma, Wilms' tumor, brain tumors, and neuroblastoma [1]. Neurotoxicity is the dose-limiting toxic effect of vincristine. Manifestations of the peripheral sensory and motor neuropathy include loss of deep tendon reflexes, neuritic pains, paresthesias, and a drop of wrist and foot. Cranial motor nerves may be affected, and autonomic nerve involvement may be responsible for constipation, paralytic ileus, or urinary retention. The toxicity is usually related to the amount of the dose and is more common on a weekly schedule; however, idiosyncrasy to the drug is known as well. In most cases, the symptoms are reversible upon withdrawal of the drug [1].

Some hereditary conditions such as Charcot-Marie-Tooth (CMT) expose the patient treated with vincristine to a higher risk of neurotoxicity [2]. CMT1 is usually an autosomal dominant trait whereby the major locus linked to it was found on chromosome 17 p11.2 [3]. In the majority of CMT1A cases, the disease segregates with a 1.5 Mb duplication, involving loci D17S122, D17S125, and D17S61 [4,5]. The presence of the duplication can be demonstrated by a dosage difference in a quantitative Southern blot analysis.

We describe a child who developed severe peripheral neurotoxicity during vincristine treatment for Ewing's sarcoma and was found to suffer from CMT1A based on molecular studies. Future implications of this finding regarding vincristine treatment are discussed.

CASE REPORT

A 16-year-old male presented with a huge pelvic tumor involving the right pubis and ischcium, which was diagnosed as Ewing's sarcoma. On examination, severe limitation in movement of the right hip was noted. The

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rest of the examination, including a neurological status by a pediatric hemato-oncologist, was normal. Blood count showed mild anemia with Hb 10.6g/dL, sedimentation rate of 123/135, and slightly elevated LDH levels. A full metastatic workup showed only one pulmonary metastasis. Treatment was initiated with vincristine 2 mg/m^2 (maximal dose 2 mg), cyclophosphamide 1.2 g/m^2, adriamycin 75 mg/m^2, alternating with etoposide 100 mg/m^2/d and ifosfamide 1.2 g/m^2/d for 5 days.

The first course of treatment resulted in an immediate relief of the pain from which the boy had suffered. However, at the same time he developed extreme weakness of the peroneal muscles and a slapping storklike gait. In the upper extremities, weakness and atrophy were first limited to the small muscles of the hand, but later spread to the forearm. The face, trunk, and proximal muscles were spared. Sensation was basically intact except for very mild vibratory and positional sense reduction over the distal portions of the extremities. The ankle reflexes were lost, whereas other deep-tendon reflexes were preserved. The plantar responses were difficult to elicit. A few weeks later he developed a pes cavus deformity. No responses were obtainable from any sensory nerves (axonal damage), and motor nerve conduction velocities along the peroneal and tibial nerves were markedly slowed (12 m/s), in the demyelinative range. The neuropathy, attributed to the single dose of vincristine that the patient received, persisted in spite of the fact that no further vincristine was administered during a follow-up of 1 year. Complete clinical and rentgenological remission was induced 5 months following diagnosis, after which complete resection of the tumor was performed by internal hemipelvectomy followed by myeloablative high-dose chemotherapy, including carboplatinum, etopside and ifosfamide, and peripheral stem-cell transplatation.

During one of the visits to the clinic, the boy was accompanied by his father, who suffered from bilateral drop foot similar to his son. The existence of the same neurological pathology in the father prompted us to consider a dominantly inherited neuropathy such as CMT1 as a possible explanation for the boy's severe affection by vincristine. The father refused to have a nerve conduction test and attributed the limp to many years of taxi driving. A blood sample was drawn from the son and was sent for molecular analysis.

MATERIALS AND METHODS

DNA was isolated from whole blood of the patient according to standard procedure. The sample was resuspended in TE buffer (10 mM Tris-HCL, pH 8.01 nM EDTA). The DNA was digested with MspI and the fragments were separated on a 0.7% agarose gel. DNA fragments were transferred to a nylon membrane (Hybond N+ Amersham, UK) and hybridized with two polymorphic probes: pVAW412R3 (D17S125) and pEW401 (D17S61), both duplicated in CMT1A according to Raeymaekrs et al. [5,6]. Probe pVAW412R3 detects two polymorphic MspI alleles of 10.5kb and 5.4kb, and probe pEW401 detects two polymorphic Msp alleles of 5.5kb and 4.4kb [7]. Dosage difference between the alleles in the heterozygote individuals was assessed visually.

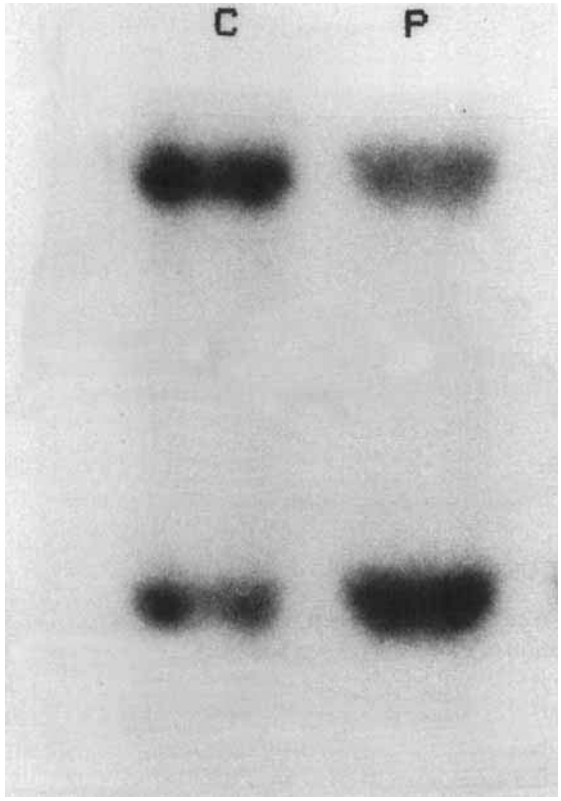

Fig. 1. Autoradiogram obtained after hybridization with probe pVAW412R3, of a MspI Southern blot. The two bands correspond to the 10.5 KB and 5.4 KB MspI alleles. In the patient (P) it can be seen that the 5.4 KB allele is more intense than the 10.5 KB allele. C, control; P, patient.

RESULTS

Figure 1 shows the results of MspI digested DNA hybridized with probe pVAW412R3. Different densities can be observed between the two alleles. The lower band, 5.4kb allele, is more intense than the higher 10.5kb band and represents two copies of this allele. Densitometry of the autoradiograph is also presented supporting measurable amplification of the lower band (Fig. 2). The result was confirmed with the pEW401 probe showing a difference in the intensity between the 4.4 and 5.5 kb alleles (data not shown).

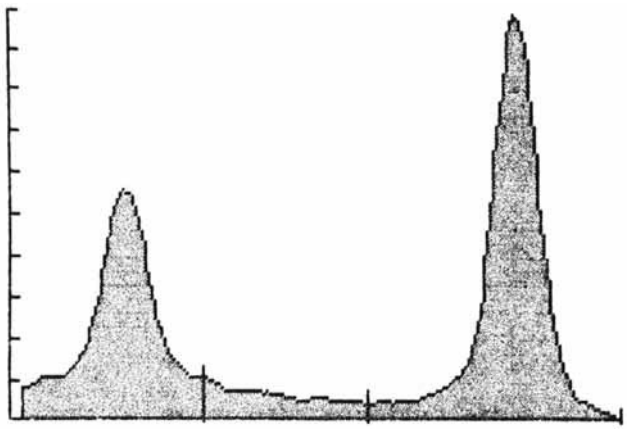

Fig. 2. Densitometry of the autoradiogram (Fig. 1) indicating that the patient (P) has a measurable amplification of the lower band.

DISCUSSION

An association between vincristine treatment and deterioration of CMT was described in only one case [2]. This case is unusual because the vincristine triggered the deterioration or the expression of an asymptomatic situation. The facts that the patient was completely asymptomatic and his neurological examination was normal are not entirely surprising in view of the fact that only 10% of affected persons with CMT1 seek medical consultation for symptoms related to the disease, either because they have few or no symptoms or they have become accustomed to their symptoms [8]. In most such cases, physical examination reveals only very mild weakness of reflexes, which may skip the attention of a pediatric hemato-oncologist. The immediate onset of neuropathy after one dose of vincristine prompted us to relate it to drug toxicity, although the initial electrophysiologic data were compatable with CMT and not isolated vincristine neuropathy, because of the slow nerve conduction velocity. Denial of the neurological deficit by the family led us to use molecular biology techniques in order to establish the diagnosis. The severe peripheral sensorimotor neuropathy, axonal and demyelinative, in a patient with molecular diagnosis of CMT is typical for a combination of drug toxicity and the basic genetic disease since the damage in CMT is demyelinative mainly.

CMT is a genetically and pathologically heterogenous group of peripheral neuropathies with an overall estimated frequency of 100×10^{-6} [9]. The clinical characteristics of the disease include distal muscle weakness and atrophy and diminished or absent deep tendon reflexes. The onset of the disease is usually in childhood or adolescence, although it may be detected by electrophysiological methods in infancy. The variation in the clinical presentation is wide. Some patients have severe distal atrophy and marked hand and foot deformities, whereas others endure only pes cavus with no distal muscle weakness or remain asymptomatic. Inheritance is autosomal dominant in most families usually with paternal imprinting, although x-linked and autosomal recessive forms of the disease have been reported [8].

Two major types of CMT were described; type 1 (CMT1) and type 2 (CMT2), both segregating as autosomal dominant traits. CMT1 is relatively common and constitutes 51% of pooled pediatric cases of hereditary peripheral neuropathies [11]. The CMT1 patients have severely slowed nerve conduction velocity (NCV), <30m/s, and extensive nerve demyelination on biopsy. The CMT2 patients have near normal NCV and nerve biopsy discloses axonal damage [9,10]. CMT1 is further divided into three entities. CMT1A, the most common type, is linked to chromosome 17p [3]. In the majority of patients with CMT1A, a duplication of 1.5 megabases in 17p11.2–12 has been identified [4,5]. The minority of patients in this subgroup, usually the more severe cases, were found to harbour mutations in the gene for the peripheral myelin protein 22 (PMP-22), which is also contained in the duplication [11–13]. CMT1B patients were found to have mutations within the gene for the major peripheral myelin protein (PO) located on chromosome 1q21-q23 [14,15]. Patients with CMT1C harbour neither mutations/duplications on chromosome 17, nor on chromosome 1.

As more and more cases of mild CMT are discovered with molecular techniques, it is suggested that the true prevalence of the disease is much higher than previously estimated (pers. commu.). Hence it may be suggested that some of the idiosyncratic reactions ascribed to vincristine are actually manifestations of deterioration of a pre-existing polyneuropathy. As the pathology in CMT is axonal and damages every nerve, we intend to do a modified, short, one or two nerve conduction test in every case where there is a family history of neuropathy to exclude CMT or any other congenital neuropathy. We also intend to cheque, by nerve conduction and molecular techniques, further cases of unusual vincristine toxicity and to offer a screening program if this turns to be a prevalent phenomenon.

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